

(12) **UK Patent Application** (19) **GB** (11) **2 374 071** (13) **A**

(43) Date of A Publication 09.10.2002

(21) Application No 0108775.8

(22) Date of Filing 06.04.2001

(71) Applicant(s)

Thomas Swan & Co Ltd  
(Incorporated in the United Kingdom)  
Crookhall, Consett, Co Durham, DH8 7ND,  
United Kingdom

(72) Inventor(s)

Stephen Keith Ross  
Nicola Jane Meahan  
Martyn Poliakoff  
Daniel N Carter

(74) Agent and/or Address for Service

Urquhart-Dykes & Lord  
8th Floor, Tower House, Merriion Way, LEEDS,  
LS2 8PA, United Kingdom

(51) INT CL<sup>7</sup>

C07C 45/62 47/228 49/403

(52) UK CL (Edition T )

C2C CAH CTB CUE C22Y C220 C221 C225 C226 C227  
C248 C259 C30Y C304 C350 C351 C353 C386 C43X  
C625 C776

(56) Documents Cited

WO 2002/002218 A1  
Chem. Abs. 128:36338  
Chemical Engineering Science (1997), 52(21/22)  
4163-4169 ISSN : 0009-2509  
Chem. Abs. 126:344671  
Ind. Eng. Chem. Res. (1997), 36(7), 2626-2633 ISSN :  
0888-5885

(58) Field of Search

DATA-BASE : CAS-ON-LINE, WPI, EPODOC, PAJ

(54) Abstract Title

**Hydrogenation reactions using supercritical fluids**

(57) The present invention relates to a continuous process for carrying out hydrogenation of a substrate in the presence of a supercritical fluid such that more than one phase is present in the reaction medium. The process leads to improved yields and selectivity of the desired hydrogenated product.

GB 2 374 071 A

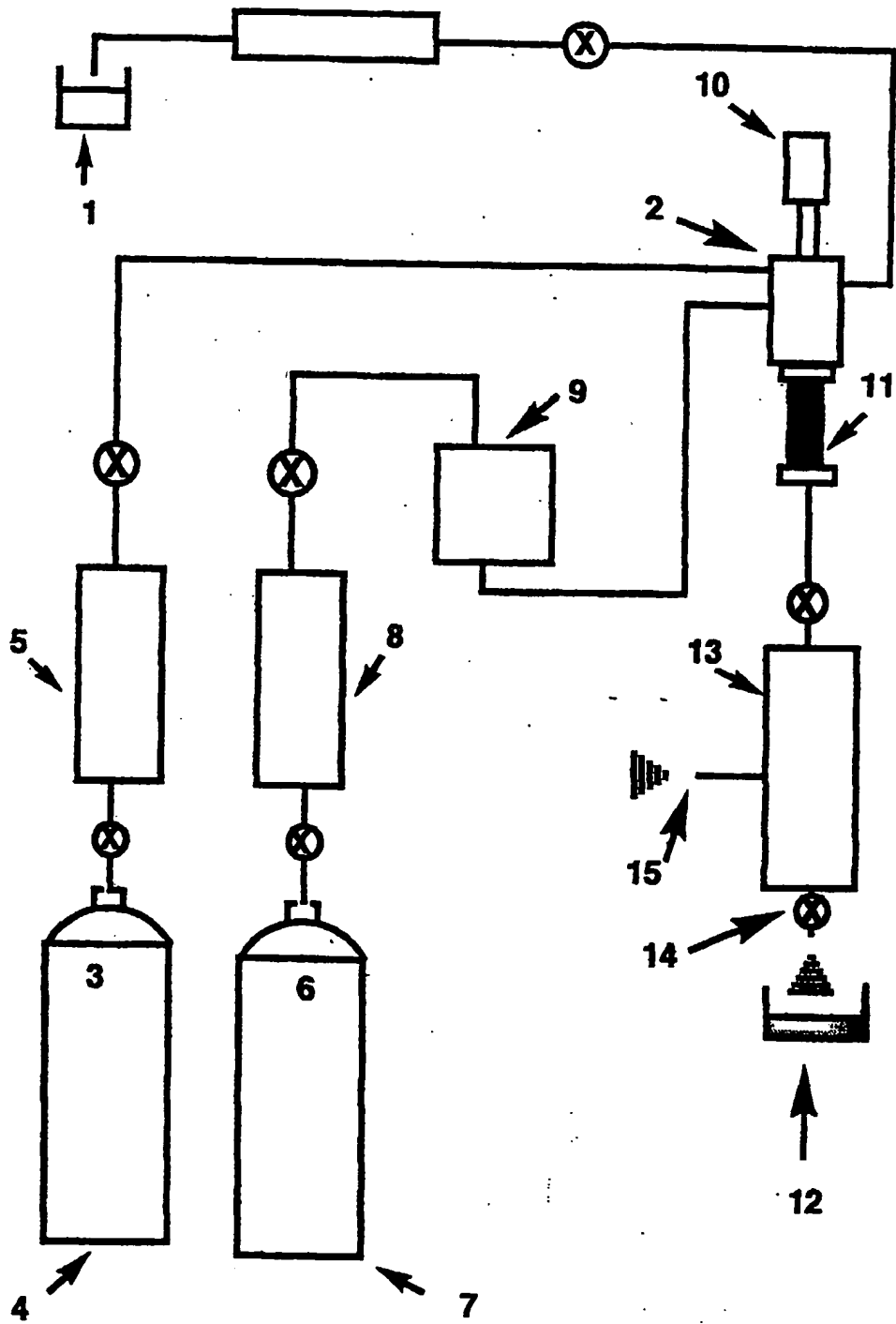


Figure 1

SUPERCRITICAL HYDROGENATION

The present invention relates to a method of carrying out a chemical reaction, which involves hydrogenation of a substrate using a heterogeneous catalyst under conditions of continuous flow in a continuous flow reactor. The hydrogenation is performed in the presence of a supercritical fluid.

10 The use of supercritical fluids in hydrogenation reactions using a heterogeneous catalyst is already well reported, for example in WO97/38955. The use of supercritical fluids in a continuous flow reactor for carrying out hydrogenation reactions is exemplified in  
15 WO 9522591, WO 9601304 and WO 97/38955. In all these patent publications, the reactions are carried out in a substantially homogeneous single phase wherein the density of the supercritical fluid is such that it is sufficient to ensure that the reactants are  
20 substantially in a single phase. The rationale for the single phase has been that this is required to eliminate Mass Transport problems for the hydrogen and so give good reaction conversion/selectivity.

25 The single phase may be obtained by working at high pressure or at a low concentration of substrate in the fluid which in either case makes industrial processes less economic than if this reaction could simply be achieved with a mixed phase system. In the current  
30 system, products have to be separated from the supercritical fluid (SCF) by multiple decompression stages. This necessitates the liquifying and recompression of the supercritical fluid, often carbon dioxide, before it can be re-circulated for further  
35 reaction. Furthermore, many amines (mainly primary and secondary organic amines, but not exclusively such

amines) react with supercritical carbon dioxide to form solid carbamates, which may precipitate within the flow system. To overcome this shortfall a co-solvent, for example methanol, must be added to the SCF, which may transfer the solid into the SCF phase. The use of many co-solvents is better avoided due to their environmental toxicity, high flammability and the requirement for further separation. This applies particularly if use is made of a flammable fluid such as a hydrocarbon or an environmentally toxic fluid such as a halocarbon.

According to the present invention in its broadest aspect, there is provided a process for the hydrogenation of a hydrogenatable substrate which is carried out in a continuous flow reactor as a mixed phase system over a heterogeneous catalyst, which system comprises one or more substrates, hydrogen or a hydrogen transfer agent and one or more products and optionally a co-solvent and includes a supercritical fluid, in which system at least one substance selected from substrate(s), product(s) and co-solvent forms a separate phase from said supercritical fluid.

Limited work has been carried out on trying to use biphasic media such as with hydrogenations in aqueous/supercritical media (Chem. Commun, 2000, 941-2). However this required a batch process and the use of homogeneous catalysts which does not lend itself to a continuous process and, as additional surfactants were required, the process becomes less efficient suffering from separation and purification problems. Furthermore it was also shown not to be a generally industrially applicable process. Three further papers (Catalysis Today 48 (1999) 337, Chem. Eng. Science Vol 52 No 21/22 pp4163 and Ind. Eng. Chem. Res. 1997, 36,

262) discuss the use of 3-phase hydrogenation in supercritical carbon dioxide. However these papers, aimed at generating mathematical models and not industrial processes, do not disclose the actual  
5 chemical reaction carried out and with conversions less than 67 % for the one model reaction discussed do not lead one to believe that such a system can be beneficial or useful with respect to carrying out hydrogenations with good selectivity or conversions.  
10 Furthermore these papers do not suggest that this could be carried out for other molecules and the phase behaviour is by model prediction (Aspen Plus). Experience has made it clear to the present inventors that this is not always reliable with respect to  
15 supercritical fluids.

We have surprisingly discovered since working on the invention of our previous patent publication (WO 97/38955) that it is possible to carry out to  
20 beneficial effect reactions involving hydrogenation in a system that is not homogenous, and also in which the density of the fluid is not sufficient to give a single phase. Such reactions enable high conversion and high selectivity to be achieved provided the fluid is  
25 sufficiently well mixed. In such cases the supercritical fluid is used not to provide a single phase and eliminate the mass transport boundary but is thought to act by reducing the viscosity of the reaction system sufficiently to effect good mixing with  
30 a similar result.

Even more surprising and contrary to the opinion of those skilled in the art of supercritical fluids is the fact that supercritical nitrogen, which has a density  
35 too low to form a single phase with the organic substrates, can still be used to give excellent

hydrogenation conversions and control of selectivity. This concept is not disclosed in any of the above mentioned literature or patents.

5 This is particularly relevant industrially as amines and nitro compounds (as reactants or products) can be mixed with supercritical nitrogen and hydrogenated without reacting with the supercritical fluid and without reverting to a fluid that is flammable or  
10 highly toxic to the environment if exposed thereto. Furthermore the use of mixed phase hydrogenation simplifies the design of chemical manufacturing plant in that no decompression stages are required for collection of the product, so that the plant may be  
15 operated at a constant pressure. This reduces the capital and operating costs, making the process more economically viable.

20 This system therefore gives all the benefits outlined in WO97/38955 but with simplified equipment and does not require the high pressures required to give a single phase. It also means that a higher loading of substrate to fluid can be used than was previously thought possible. In one embodiment, solid substrates  
25 which cannot be added as melts can be added dissolved in a co-solvent. This may give rise to even more complex behaviour yet still gives good conversion and selectivity.

30 The present invention effects hydrogenation of a substrate under conditions in which a fluid which is supercritical is present. The term "supercritical" is used herein to denote a fluid which is above its critical temperature and pressure or at conditions  
35 below supercritical at which the density of the fluid is sufficient to ensure that one but not all of the

reactants and/or products and/or added co-solvent, if any, is/are substantially in a single phase with said fluid, and wherein the viscosity of the reaction system is reduced sufficiently to enable good mixing to be achieved and hence obtain the required hydrogenation product. The catalyst bed and/or an additional pre-mixer can achieve the mixing.

By the term "hydrogenation" as used herein is meant any reaction in which hydrogen or an isotope of hydrogen (e.g. deuterium) or a hydrogen transfer agent (e.g. formic acid) is an active agent. Such reactions include hydrogenolysis, saturation reactions, reductive alkylation/amination and also hydroformylation, as all these require addition of hydrogen to a substrate. The substrate itself typically, but not exclusively, is selected from alkene, alkyne, lactone, anhydride, amide, lactam, Schiff's base, aldehyde, ketone, alcohol, nitro, hydroxylamine, nitrile, oxime, imine, azine, hydrazone, azide, cyanate, isocyanate, thiocyanate, isothiocyanate, diazonium, azo, nitroso, phenol, ether, furan, epoxide, hydroperoxide, ozonide, peroxide, arene, saturated or unsaturated heterocyclic, halide, acid halide, acetal and ketal.

The process of this invention preferably comprises the steps of:

- (a) mixing a supply of a supercritical fluid containing a substrate with a supply of hydrogen (the substrate may be added in an additional co-solvent if it cannot be added as a liquid or gas)
- (b) adjusting the temperature and pressure to just below or above the critical point of the fluid and
- (c) further raising the temperature if required to the desired reaction temperature
- (d) exposing the mixture to a heterogeneous catalyst

to facilitate reaction  
(e) isolating the reaction product (the mode of  
isolation will be determined by the scale of  
operation and the choice of supercritical fluid  
5 and the physical form of the reaction product).

In an additional embodiment, two or more reaction zones  
can be placed in series to effect different  
hydrogenation reactions as exemplified in WO97/38955  
10 (except that in this case the reactions are all carried  
out in a mixed phase system).

The catalysts used can be any heterogeneous catalysts,  
the choice of metal and support depending on the  
15 identity of the functional group(s) to be hydrogenated.  
The catalyst used in the process of this invention  
preferably comprises a carrier and a metal selected  
from platinum, nickel, palladium or copper or a  
combination thereof, and optionally a promoter.

20 Particularly favoured media to have in the reaction  
system as component in a supercritical condition  
include carbon dioxide, sulphur dioxide, nitrogen,  
alkanes such as ethane, propane and butane, alkenes,  
25 ammonia, and halocarbons such as  
trichlorofluoromethane, dichlorofluoromethane,  
dichlorodifluoromethane, chlorotrifluoromethane,  
bromotrifluoromethane, trifluoromethane, and  
hexafluoroethane. The choice of supercritical fluid is  
30 only limited by the engineering constraints but  
favoured fluids are carbon dioxide and nitrogen. Other  
fluids such as halocarbons or hydrocarbons or a mixture  
of fluids could also be used.

35 The reaction medium may be a mixture of two or more  
fluids having critical points which do not require



commercially unacceptable conditions of temperature and pressure in order to achieve the necessary conditions for reaction according to the present invention. For example, mixtures of carbon dioxide with an alkane such  
5 as ethane or propane, or a mixture of carbon dioxide and sulphur dioxide may be employed close to or above their theoretical critical points.

Insofar as the present invention extends to  
10 hydroformylation (also known as the "oxo process") this is used for large-scale production of aliphatic aldehydes and alcohols from olefins (alkenes) using cobalt- or rhodium-based homogeneous catalysts. In general, the hydroformylation reaction involves  
15 reaction of an alkene or alkyne with a mixture of carbon monoxide and hydrogen over a catalyst at high pressure to produce a carbonyl compound. Mixtures of hydrogen and carbon monoxide are frequently referred to as synthesis gas or syn gas.

20 Further details of hydroformylation techniques which can be adapted in accordance with the present invention appear in WO00/01651. In particular, it is preferred that the catalyst comprises a support and a metal or  
25 metal complex in which the metal is selected from: platinum, nickel, palladium, cobalt, rhodium, iridium, iron, ruthenium, and osmium, and the catalyst optionally includes a promoter. Rhodium is a particularly preferred metal.

30 As with the single phase reactions of WO 97/38955, the multiphase reactions of this invention can be used to achieve selectivity in respect of reaction product when the substrate is capable of yielding more than one  
35 reaction product. Prior experiment may be carried out, varying one or more of temperature, pressure, flow

rates, H<sub>2</sub> concentration for a given catalyst to produce products differing as to product identity, as well as product, yield, and, with a set of conditions then defined for a particular product, working in accordance with such conditions.

In the context of the present invention, the lower limits of the conditions suitable for supporting the hydrogenation reaction are conditions of temperature and pressure at or just below the critical point of the fluid. The upper limit is governed by limitations of the apparatus.

The present invention will now be described by way of the accompanying figure which is a schematic representation of a continuous flow reactor and the examples listed below.

Substrate 1, dissolved in an appropriate solvent if it is a solid, is pumped into mixer 2 which may be a mechanical or static mixer where it is mixed with fluid 3 which is to be supercritical and which has been delivered from reservoir 4 via pump 5. Hydrogen 6 is delivered from reservoir 7 via compressor 8 and a dosage unit 9 to mixer 2. The hydrogen pressure is typically 20-50 bar higher than the pressure at which fluid 3 is supplied. The hydrogen is added via a switching valve or similar control to give the required hydrogen to substrate ratio, the actual ratio being dependent on the particular hydrogenation reaction being carried out. The temperature and /or pressure of the reaction mixture is adjusted to a temperature and pressure just below, at or above the critical point of the fluid 3 as required. Heating means 10 is provided for this purpose. This control of conditions can also be achieved by heating/cooling the reactor or a

combination of both. The mixture is then passed into reactor 11 which contains a catalyst (not shown) fixed on a suitable support. After an appropriate residence time the mixture is passed into pressure reduction unit 13 and the product removed via take-off tap 14. The flow rate of the mixture through the reactor is controlled by a valve (not shown) in pressure reducer 13. Fluid 3, together with any unconsumed hydrogen is vented through relief pipe 15 to atmosphere. This description is applicable particularly to the illustrated laboratory apparatus, which can obviously be changed to allow for recycling on the larger scale.

#### Examples

The following examples show typical hydrogenation by way of example only. These are not necessarily optimum and do not imply limitations to the reaction conditions and equipment. The reactions were carried out over 2% Pd on alumina or 5 % Pd on Deloxan catalysts in a 5 ml fixed bed reactor.

Example 1

Hydrogenation of cinnamaldehyde in the presence of supercritical nitrogen

5 Reaction took place in a mixed phase system (0.5 ml/min cinnamaldehyde in 0.65 L/min flow with 2.75 equivalents of hydrogen @120 bar = cinnamaldehyde in the supercritical fluid) following the procedure described  
10 with reference to the accompanying drawing. It gave 99% conversion with greater than 88% selectivity for the  $\alpha,\beta$ -dihydrocinnamaldehyde at 70°C. The system was confirmed to be multiple phase by visual inspection in a view cell with mixer under the defined temperatures  
15 and pressures.

Example 2

(a) Single Phase Hydrogenation of isophorone in the presence of supercritical Carbon Dioxide

20 Isophorone was reacted with hydrogen in a single phase (0.5ml/min isophorone in 6.2 L/min flow of carbon dioxide with 2.75 equivalents of hydrogen at 120 bar = 8% isophorone in the supercritical fluid) and the reaction yielded 99.2% of the  
25 trimethylcyclohexanone at 70°C.

(b) Multiple Phase hydrogenation

30 The same reaction as in (a) was carried out in a mixed phase system (1 ml/min isophorone in 1.2 L/min flow with 2.75 equivalents of hydrogen at 120 bar = 30% isophorone in the supercritical fluid) and yielded 99.3% of the trimethylcyclohexanone at 70°C. Hence a mixed phase system can be as good as the single phase  
35 system.

CLAIMS

1. A process for the hydrogenation of a hydrogenatable substrate which is carried out in a continuous flow reactor as a mixed phase system over a heterogeneous catalyst, which system comprises one or more substrates, hydrogen or a hydrogen transfer agent and one or more products and optionally a co-solvent and includes a supercritical fluid, in which system at least one substance selected from substrate(s), product(s) and co-solvent forms a separate phase from said supercritical fluid.
2. A process as claimed in claim 1, wherein there is employed a substrate selected from alkene, alkyne, lactone, anhydride, amide, lactam, Schiff's base, aldehyde, ketone, alcohol, nitro, hydroxylamine, nitrile, oxime, imine, azine, hydrazone, azide, cyanate, isocyanate, thiocyanate, isothiocyanate, diazonium, azo, nitroso, phenol, ether, furan, epoxide, hydroperoxide, ozonide, peroxide, arene, saturated or unsaturated heterocyclic, halide, acid halide, acetal and ketal.
3. A process claimed in claim 1 or 2, wherein one or more of temperature, pressure, flow rates and  $H_2$  concentration is/are varied for a given catalyst to obtain a set of conditions which defines a selected product and the process is then carried out under said set of conditions to produce that selected product.
4. A process as claimed in any preceding claim wherein the supercritical fluid is carbon dioxide, nitrogen, an alkane, an alkene, ammonia, a halocarbon or a mixture of these.

5. A process as claimed in any preceding claim wherein the catalyst is a supported metal catalyst.

5 6. A process according to any preceding claim, wherein the catalyst comprises a carrier and a metal selected from platinum, nickel, palladium, copper and combinations thereof, and optionally a promoter.

10 7. A process according to any previous claim, wherein the source of hydrogen is an isotope of hydrogen or a hydrogen transfer reagent.

15 8. A process claimed in any preceding claim, which is a hydroformylation process carried out on an alkene or an alkyne.

20 9. A process according to claim 8 wherein the catalyst comprises a support and a metal or metal complex in which the metal is selected from; platinum, nickel, palladium, cobalt, rhodium, iridium, iron, ruthenium, or osmium; and the catalyst optionally includes a promoter.



INVESTOR IN PEOPLE

Application No: GB 0108775.8  
Claims searched: 1-9

13

Examiner: S.I. AHMAD  
Date of search: 29 May 2002

## Patents Act 1977 Search Report under Section 17

### Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T):

Int Cl (Ed.7):

Other: Data-base: Cas-on-line, WPI, EPODOC, PAJ

### Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	WO 02/02218 A1 UNIV ST. ANDREWS(whole document)	ALL
X	Chem. Abs. 128:36338 Chemical Engineering Science (1997), 52(21/22), 4163-4169 ISSN : 0009-2509	"
X	Chem. Abs. 126:344671 Ind. Eng. Chem. Res. (1997), 36(7), 2626-2633. ISSN:0888-5885	"

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.